

## AMENDMENT

### Listing of Claims

The following listing of claims replaces all previous listings or versions thereof:

1. (Presently amended) A method for producing bone *ex vivo*, comprising the steps of:
  - a) obtaining an osteogenic cell or bone precursor cell;
  - b) culturing said cell under serum free conditions in the presence of one or more osteogenic growth factors and at cell densities which produce a bone cell spheroid of approximately 3000 to 100,000 cells; and
  - c) ~~maintaining the cell cultures at cell densities that allow the formation of a said~~ bone cell spheroid under conditions which produce bone;

~~whereby bone is formed by cells~~ within said bone cell spheroid.
2. (Original) The method of claim 1, wherein the osteogenic cell or bone precursor cell is of human origin.
3. (Original) The method of claim 1, wherein the osteogenic cell or bone precursor cell is of bovine origin.
4. (Original) The method of claim 1, wherein the osteogenic cell or bone precursor cell is of equine origin.
5. (Original) The method of claim 1, wherein the osteogenic cell or bone precursor cell is of canine origin.
6. (Original) The method of claim 1, wherein the osteogenic cell or bone precursor cell is of feline origin.

7. (Original) The method of claim 1, wherein the osteogenic cell or bone precursor cell is of murine origin.
8. (Original) The method of claim 1, wherein the osteogenic cell or bone precursor cell is of rat origin.
9. (Original) The method of claim 1, wherein the osteogenic cell or bone precursor cell is of chick origin.
10. (Original) The method of claim 1, wherein the growth factor is TGF- $\beta$ 1, TGF- $\beta$ 2, TGF- $\beta$ 1.2, VEGF, insulin-like growth factor I or II, BMP2, BMP4, or BMP7.
11. (Original) The method of claim 1, wherein the growth factor is parathyroid hormone, calcitonin, interleukin-6, or interleukin-11.
12. (Original) The method of claim 1, further comprising purifying the osteogenic cell or bone precursor cell by physico-chemical separation techniques.
13. (Original) The method of claim 12, wherein the physico-chemical separation technique is equilibrium density separation.
14. (Original) The method of claim 1, further comprising purifying the osteogenic cell or bone precursor cell by immuno-affinity isolation.
15. (Original) The method of claim 14, wherein the immuno-affinity isolation utilizes immune adhesion, immuno-column chromatography, or fluorescence-activated cell sorting.
16. (Original) The method of claim 14, wherein the immuno-affinity isolation utilizes antibodies to osteocalcin, osteonectin, or alkaline phosphatase, or combinations thereof.

17. (Original) The method of claim 1, wherein said cell-densities at the initiation of the culture are from about  $1.0 \times 10^3$  to about  $1 \times 10^6$  cells per  $\text{cm}^2$ .
18. (Original) The method of claim 1, further comprising implanting the cells *in vivo*.
19. (Presently amended) A method of providing bone tissue to a mammal, comprising obtaining a bone cell spheroid of approximately 3000 to 100,000 bone cells and implanting the bone cell spheroid into said mammal.
20. (Original) The method of claim 19, wherein the bone cell spheroid is implanted in one or more of alginate gels, collagen gels, or fibrin gels.
21. (Original) The method of claim 19, wherein the bone cell spheroid is implanted in one or more of polylactic acid, polyglycolic acid or PGLA.
22. (Original) The method of claim 19, wherein the bone cell spheroid is implanted in or in conjunction with hydroxyapatitic, other apatitic compounds, devitalized animal bone, devitalized human bone, or porous ceramic structures.
23. (Original) The method of claim 19, wherein the implantation is made in conjunction with orthopedic surgery and/or orthopedic devices, such as hip implants, knee implants, or spinal fusions.
24. (Original) The method of claim 19, wherein the implantation is made in conjunction with oral surgery and/or dental implants.
25. (Original) The method of claim 19, wherein the implantation is made in conjunction with plastic surgery.

26. (Original) The method of claim 19, wherein the implantation is in conjunction with periodontal repairs.
27. (Original) The method of claim 19, wherein the implantation is into bone-forming tissue.
28. (Original) The method of claim 19, wherein the implantation is into a wound.
29. (Original) The method of claim 19, wherein the mammal has a bone disease such as osteoporosis, Vitamin D deficiency, Osteitis deformans, Von Recklinghausen's Disease.
30. (Presently amended) A method for producing bone *ex vivo*, comprising the steps of:
- a) obtaining an osteogenic cell or bone precursor cell;
  - b) culturing said cell under serum free conditions in the presence of one or more osteogenic growth factors and at cell densities which produce a bone cell spheroid of approximately 3000 to 100,000 cells;
  - c) ~~maintaining the cell cultures at cell densities that allow the formation of a bone cell spheroid, whereby bone is formed by cells within said bone cell spheroid~~ under conditions which produce bone; and,
  - d) removing the cellular elements from the formed bone ~~cell spheroid~~ and using resulting bone *in vivo*.
- 31-34. (Canceled)
35. (Withdrawn) A method for identifying a modulator of bone formation, bone repair and/or bone disease, comprising the steps of:
- a) obtaining an osteogenic cell or bone precursor cell;
  - b) culturing said cell under serum free conditions in the presence of a candidate modulator in the absence of one or more osteogenic growth factors;

- c) measuring bone cell spheroid formation; and
  - d) comparing the formation of bone cell spheroid with that observed in the absence of the modulator.
36. (Withdrawn) The method of claim 35, further comprising a step of culturing an osteogenic cell or bone precursor cell in the presence of one or more osteogenic growth factors.
37. (Withdrawn) A method for producing a modulator of bone formation, bone repair and/or bone disease comprising the steps of:
- a) obtaining an osteogenic cell or bone precursor cell;
  - b) culturing said cell under serum free conditions in the presence of a candidate modulator in the presence of one or more osteogenic growth factors;
  - c) measuring bone cell spheroid formation;
  - d) comparing the formation of bone cell spheroid with that observed in the absence of the modulator; and
  - e) producing a modulator so identified.
38. (Presently amended) A bone cell spheroid made by the process of:
- a) obtaining an osteogenic cell or bone precursor cell;
  - b) culturing said cell under serum free conditions in the presence of one or more osteogenic growth factors and at cell densities which produce a bone cell spheroid of approximately 3000 to 100,000 cells; and
  - e) ~~maintaining the cell cultures at cell densities that allow the formation of a bone cell spheroid,~~
- ~~whereby bone is formed by cells within said bone cell spheroid.~~